TOWARDS ARGININE MIMETICS

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Introduction

Arginine is a naturally occurring basic amino acid, that is involved in a large number of important protein-protein and protein-nucleic acid interactions. The ability of the protonated side chain of arginine to form hydrogen bonds and "salt bridges" with aspartic and glutamic acid residues in proteins, and with phosphates and bases in DNA/RNA; thus stabilizing elements of protein structure has been widely observed.

In addition, arginine is frequently found alongside cleavage sites of substrates and inhibitors of trypsin-like serine proteases, such as thrombin, Factor Xa, and Dengue NS3 protease,[1] and also in novel antagonists of G Protein-Coupled Receptors such as the plasma protein C5a.[2]

1.Brinkworth, R.I., Fairlie, D.P., Leung, D., and Young, P.R., *Journal of General Virology*, **1999**, *80*, 1167.
2.Finch, A. M.; Wong, A. K.; Wadi, S. K.; Paczkowski, N. J.; Fairlie, D. P.; Taylor, S. M. *J. Med. Chem.* **1999**, *42*, 1965.

The problem

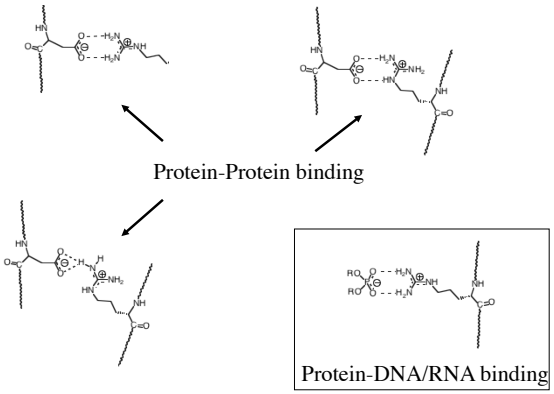
The highly polar and charged side chain of arginine is often an undesirable feature in drug design and discovery programs. Problems with bioavailability and poor membrane permeability have historically resulted in poor progression of the thousands of known enzyme inhibitors into the clinic and as human therapeutics.[3]

Arginine also possesses a highly flexible sidechain, which may require the expenditure of energy to adopt an enzyme-binding configuration.

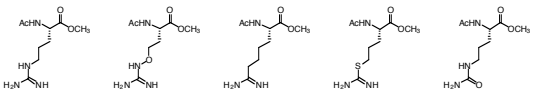
Arginine displays complex side-reactions in solution-phase syntheses, complicating product outcomes and purification procedures.

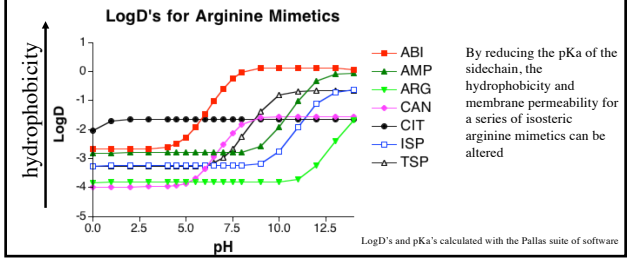
3. Leung, D., Abbenante, G. and Fairlie, D.P., *J. Med. Chem.*, **2000**, *43*, 305.

Binding Modes of Arginine



Effect of pKa Modification



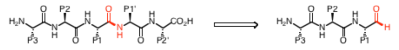


By reducing the pKa of the sidechain, the hydrophobicity and membrane permeability for a series of isosteric arginine mimetics can be altered

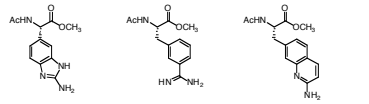
LogD's and pKa's calculated with the Pallas suite of software

Modification of side chain hydrophobicity

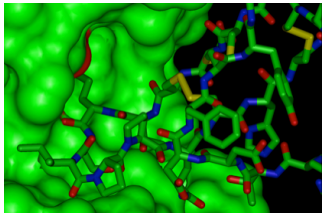
Thrombin-like serine protease inhibitors have traditionally involved the use of a peptide fragment derived from the P1-P3 sequence of endogenous substrates, with the scissile bond being replaced with an electrophilic isostere such as aldehyde or trifluoromethyl ketones.

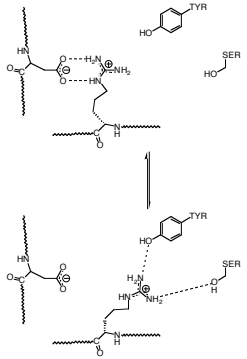


Extensive work in our laboratories and others, is being directed towards the synthesis of compounds with more rigid and hydrophobic side chains and also to the synthesis of arginine mimetics lacking electrophilic isosteres.



Crystal Structure of Dengue NS3 Protease with bound Bowman-Birk Inhibitor





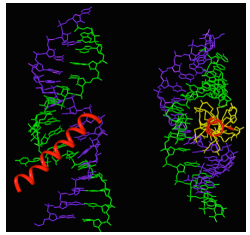
Inhibitor contains an arginine in two equally populated states; hydrogen bonding to serine and tyrosine residues in one form and in a "traditional" Type 2 bonding arrrangement with an aspartate residue in the other

Applications: HIV-REV

HIV-1 Rev is a 116 amino acid RNA-binding protein, that is responsible for transport of viral mRNA from the host nucleus to the cytoplasm. The binding domain consists of a core of 17 residues, 10 of which are Arginine.

One project within our group entails systematically altering the arginine residues within the binding domain to ultimately produce an inhibitor with improved membrane permeability. Such an inhibitor should prevent replication of HIV in infected human cells.

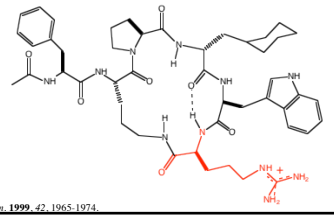
Bonding of $Rev_{34\text{-}50}$ to RNA



Scanlon, M. J. *et al.*, *Biochemistry* **1995**, *34*, 8242-8249.

Applications: C5a Antagonists

C5a is a 74 residue complement protein which is synthesized in human blood in response to infection. The interaction between C5a (in the blood) and its receptor on the surface of numerous types of cells leads to production of many cytokines and inflammatory mediators which contribute to autoimmune and inflammatory diseases such as rheumatoid arthritis, lupus, asthma, ischemia and reperfusion injury and at least 20 other inflammatory conditions. Cyclic hexapeptides have been shown in our laboratory to be potent, orally available antagonists of the C5a receptor, a member of the G Protein-Coupled receptor family. We are in the process of examining the effect on bioavailability of analogues bearing arginine mimetics.



Finch, A. M.; *et al.*, *J. Med. Chem.* **1999**, *42*, 1965-1974.